stress-induced over-expression of caveolin-1 in the cellular aging. Our recent study revealed that angiogenic growth factors, especially vascular endothelial growth factor (VEGF), downregulate catabolic activity and cellular aging, and also maintain anabolic viability in chondrocytes. We also review the underlying signal transduction pathways. Finally, we show that newly developed antioxidant C60 is a useful as a therapuetic agent sto reduce articular cartilage degeneration in the OA rabbit model.
Conclusions: Our studies reported here sought to demonstrate in the OA model *in vitro* and *in vivo* that oxidative stress is closely involved in the caritilage/chondrocyte aging and degeneration and that angiogenic growth factors may at least in part participate in the pathogenesis of OA. Also, we demenstrate that water-soluble C60 fullerene, a strong free-radical scavenger, can function as a protective agent against the catabolic stress-induced degeneration of articular cartilage.

I-20 THE APPLICATION OF PROTEOMICS IN THE STUDY OF OSTEOARTHRITIS

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Purpose: For a highly complex, multifaceted disorder such as osteoarthritis, proteomic approaches have much to offer. Biomarker "fingerprints" which indicate disease outcome, networks of molecular pathology and therapeutic targets can be filtered out from background signals with proteomic techniques.
Methods: Following closely on the heels of genomic screening, proteomic platforms have the potential to provide additional levels of understanding to the leading edge of osteoarthritic disease. Proteomic tools have the significant advantage in not precluding biomarker identity, so research strategies can be formed in an objective, "unsupervised" fashion.
Results: This talk aims to give the unitiated an overview of the technologies currently available, highlighting their assets and pitfalls. A brief history of findings to date from published proteomics studies of synovial fluid, cells and tissue will be reviewed from a variety of arthrides. The importance of formulating clinically relevant questions will form a major focus and novel strategies and sufficient powering of studies will be discussed.
Conclusions: This workshop gives the opportunity to learn of the skills now available, giving inspiration and expanding on existing knowledge. The content is pitched at scientists and clinicians with limited knowledge of global proteomic technologies and strategies and an interest in applying them in the study of osteoarthritis.

I-21 COMBINED TRANSCRIPTOME AND PROTEOME APPROACHES TO ELUCIDATE GENE EXPRESSION PATTERNS OF SYNOVIAL TISSUES AND SYNOVIAL FLUIDS FROM PATIENTS WITH RHEUMATOID ARTHRITIS VERSUS OSTEOARTHRITIS

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Purpose: With the availability of the human genome sequence and those of animal models, data driven research for unravelling the molecular grounds of Rheumatoid Arthritis (RA) and Osteoarthritis, respectively, can be considered a realistic challenge to the scientific community.
Methods: A comprehensive research strategy is presented for studying multifactorial polygenic (autoimmune) diseases, enabling the integration of multiple research efforts by so called proteomics and systems biology approaches. An integrative scientific concept is discussed of how to elucidate molecular mechanisms of complex diseases using state-of-the-art methodologies in functional and comparative genomics.
Results: RNA, protein, and peptide microarray profiles are currently obtained in cutting edge research projects producing gene signature read-outs rather than single DNA and/or protein markers. A continuous interchange of data-driven and hypothesis-driven research has been established in order to investigate the value of such "marker signatures".
Conclusions: Currently, a comprehensive study of the RNA and protein regimes is undertaken that eventually will lead to a "holistic" view of signalling pathways that are expected to reveal how the respective molecules and the cells themselves interact with each other; hopefully leading to new diagnostics and therapeutics in the future.

I-22 RHO SIGNALING PATHWAYS IN CARTILAGE DEVELOPMENT AND OSTEOARTHRITIS

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Purpose: To compare the role of Rho GTPases in the control of the chondrocyte phenotype in development and osteoarthritis.
Methods: Rho GTPase activity in chondrocytes was determined by G-LISA assay. Activities of specific Rho GTPases in chondrocytes were manipulated using pharmacological and genetic approaches. Effects of these manipulations on chondrocyte physiology in monolayer culture, organ culture and mice were investigated using a variety of techniques, including real-time PCR, histological and immunohistochemical techniques, cytoskeletal staining and proliferation assays.
Results: Our results show that RhoA through its mediators ROCK1/2 suppresses both early and late (hypertrophic) chondrocyte differentiation during cartilage development. Similarly, Rho/ROCK mediates loss of the chondrocyte phenotype in response to transforming growth factor alpha (TGFalpha), a growth factor that we have shown to be upregulated in osteoarthritic cartilage. Importantly, ROCK inhibition suppresses TGFalpha-induced breakdown of collagen II and aggrecan in articular cartilage explants. In contrast, other Rho family members, most notably Rac1 and Cdc42, promote chondrocyte maturation at multiple stages and through different mechanisms. Cartilage-specific deletion of the Rac1 gene in mice leads to severe chondrodysplasia, with reduced chondrocyte proliferation, skeletal malformations (e.g. scoliosis and kyphosis) and profound dwarfism. These effects appear to be mediated, at least in part, by altered iNOs expression and nitric oxide levels, showing a novel link between Rho GTPase and nitroc oxide signaling.
Conclusions: Our data suggest that Rho GTPases play multiple and specific roles in the control of both growth plate and articular chondrocyte physiology. They may therefore present novel targets for therapeutic interventions both for osteoarthritis and disorders of skeletal development, such as chondrodysplasias.

I-23 EPIDEMIOLOGIC EVIDENCE FOR JOINT SHAPE AS A CAUSE OF OA

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Purpose: Osteoarthritis of the hip is a common cause of pain and disability in older individuals. While the major risk factors for hip OA are both genetic and environmental, minor variations in the proximal femur or acetabular geometry have also been identified as potential risk factors for hip OA. These observations support the hypothesis that subtle variation in proximal femur/acetabular morphology may compromise the joint biomechanically and lead to hip OA. Two recent studies will be reviewed that utilized active shape modeling of the proximal femur to determine what proximal femur shapes are risk factors for hip OA.
Methods: The pelvic radiographs used for these analyses were obtained in the supine position. A baseline and follow-up radiograph was assessed for presence and severity of radiographic hip OA with either a modified Croft or a Kellgren and Lawrence method. The shape of the proximal right femur was outlined using a digitized radiograph from the baseline visit, by placing points evenly spaced points around the proximal femur. The Active Shape Modeling Program (University of Manchester, UK) was applied to the datasets to assess shapes in the femoral head, neck and shaft before, during and after the development of radiographic hip OA. Scores of shape variance, or mode scores were assigned to 10 modes of variation in each hip, and differences in mode scores were determined.
Results: Incident hip OA study: the baseline shape analysis was significantly different between RHOA cases and controls in 3 modes (3, 5, and 9) ($p < 0.001$). Mode 3 (associated with the most variance of 9%) represented a subgroup with incident RHOA characterized by a larger femoral head. Each of those three modes predicted incident RHOA with adjusted ORs of around 1.7. A separate study reported significant differences in the femoral head shape between OA cases and controls and hips with OA progression but not in the control group over time.
Conclusions: These studies and others support the hypothesis that subtle variations in the shape of the proximal femur (either the femoral head or femoral neck) and or the acetabulum appear to increase the risk of incident and progressive RHOA. Research should now be directed toward novel interventions that might be able slow the progression of hip OA in individuals with these subtle variations in hip shape.